

CR10049, the first intra-articular Src family kinase inhibitor as a long-acting symptom- and disease-modifying drug for the inflammatory OA phenotype

Luigi Giancotti, Rottapharm Biotech

Disclosure

I have no relevant financial relationship(s) with ineligible companies to disclose

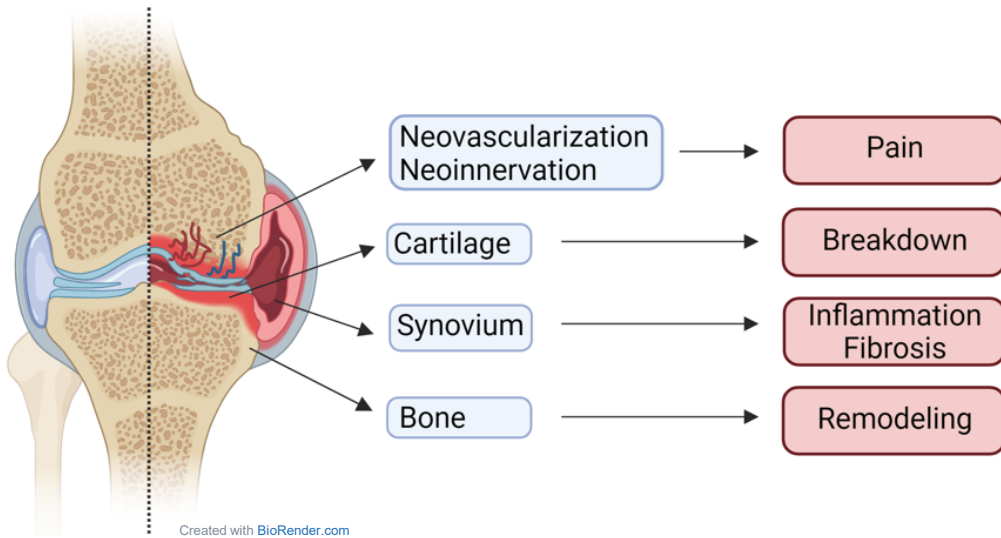
In accordance with the ACCME Standards for Integrity and Independence in Accredited Continuing Education, ACR has implemented mechanisms prior to the planning and implementation of this CME activity to identify and mitigate all relevant financial relationships for all individuals in a position to control the content of this CME activity.

Learning objectives

At the end of the presentation, participants will be able to:

- identify multi-target therapy as a promising approach in treating the inflammatory OA phenotype
- recognize that blocking key kinases involved in OA pathogenesis within the joint space can be beneficial, with good tolerability
- acknowledge that a single IA injection of CR10049 is efficacious for a long period of time

Inflammatory osteoarthritis (OA) is a whole joint disease

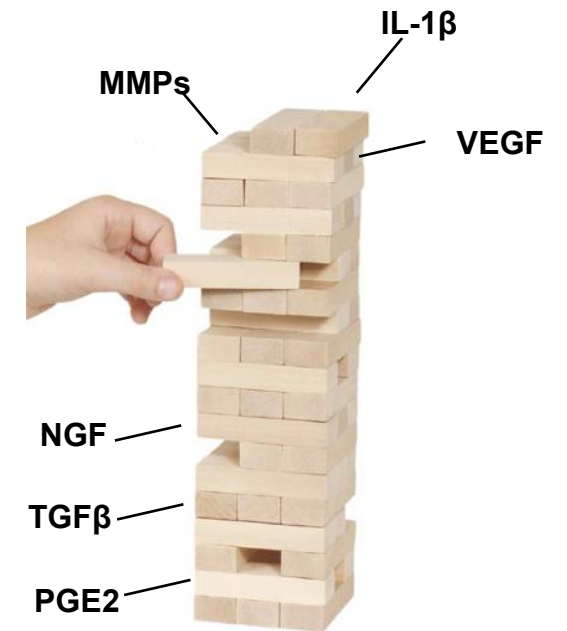


- **Many pathological features** are involved in the generation of the inflammatory and destructive events in the joint tissues affected by OA
- Lack of efficacy of compounds targeting one single component suggest **multiplicity and interaction** of factors in OA

No single brick, when eliminated, is sufficient to collapse the whole inflammatory and degradative tower



targeting **more than one pathway** is necessary to block all the pathological features of inflammatory OA

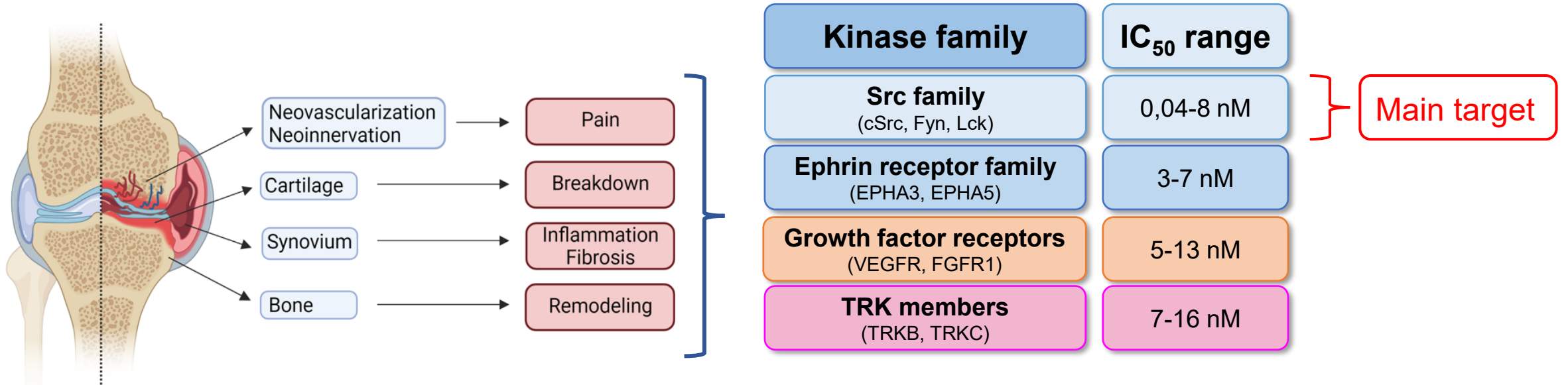


inflammatory and degradative tower

CR10049 inhibits SRC-family members in a low nanomolar range

Src family kinases members activation induces inflammation as well as degradation of cartilage and bone in the joint^(1,2,3)

CR10049 is a small molecule lead of a series of potent compounds designed to target preferentially the Src family



Kinase specificity has been tested on a panel of 159 kinases

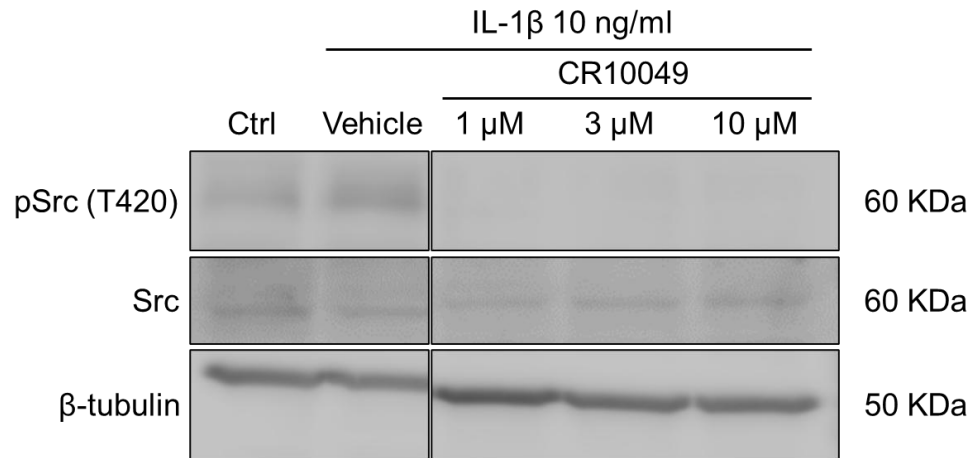
[1] Ley, 2014. JEM PMID: 25246388

[2] Novikov et al., 2021 Sci Rep. PMID: 34848799

[3] Bernard, 2018 Nat Rev Rheumatol PMID: 29760436

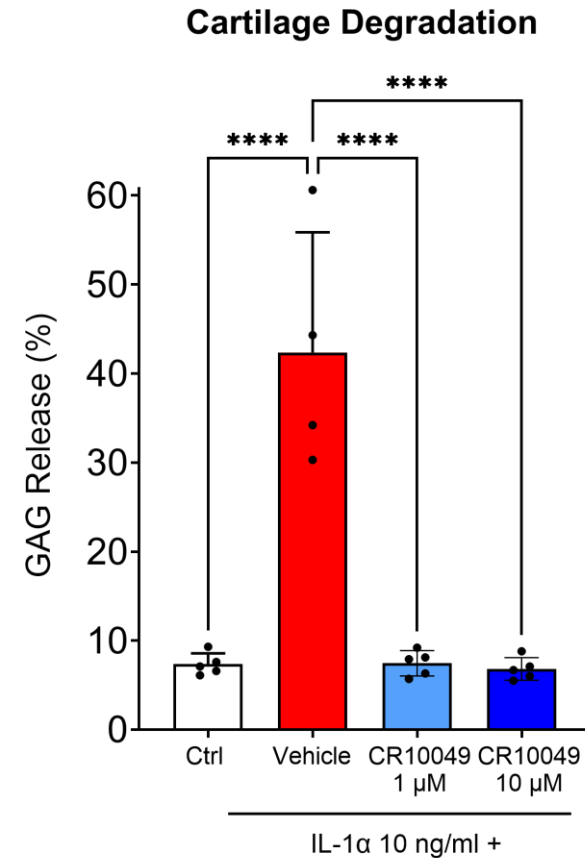
CR10049 inhibits inflammation but also degradation in *in vitro* OA models

pSrc phosphorylation and pro-inflammatory and matrix-degrading enzymes reduction in articular chondrocytes



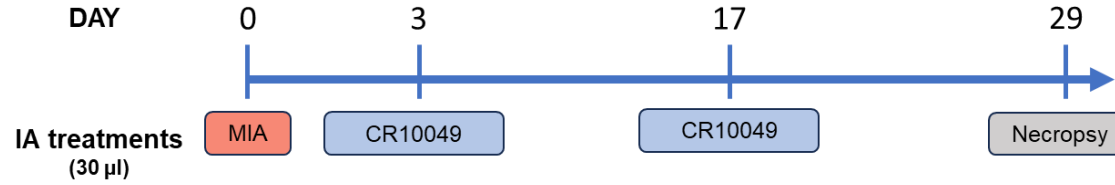
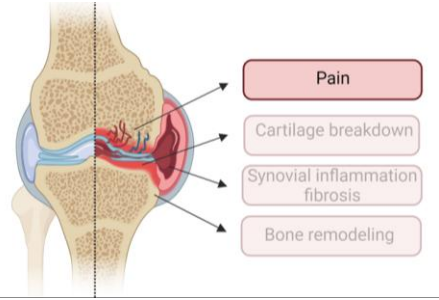
	IL-1β	IL-6	COX2	ADAMTS-5	MMP3	MMP13
CR10049 IC₅₀ (nM)	< 10	18	187	34	327	447

Articular chondrocytes were stimulated by IL-1β and gene expression was analysed by qPCR

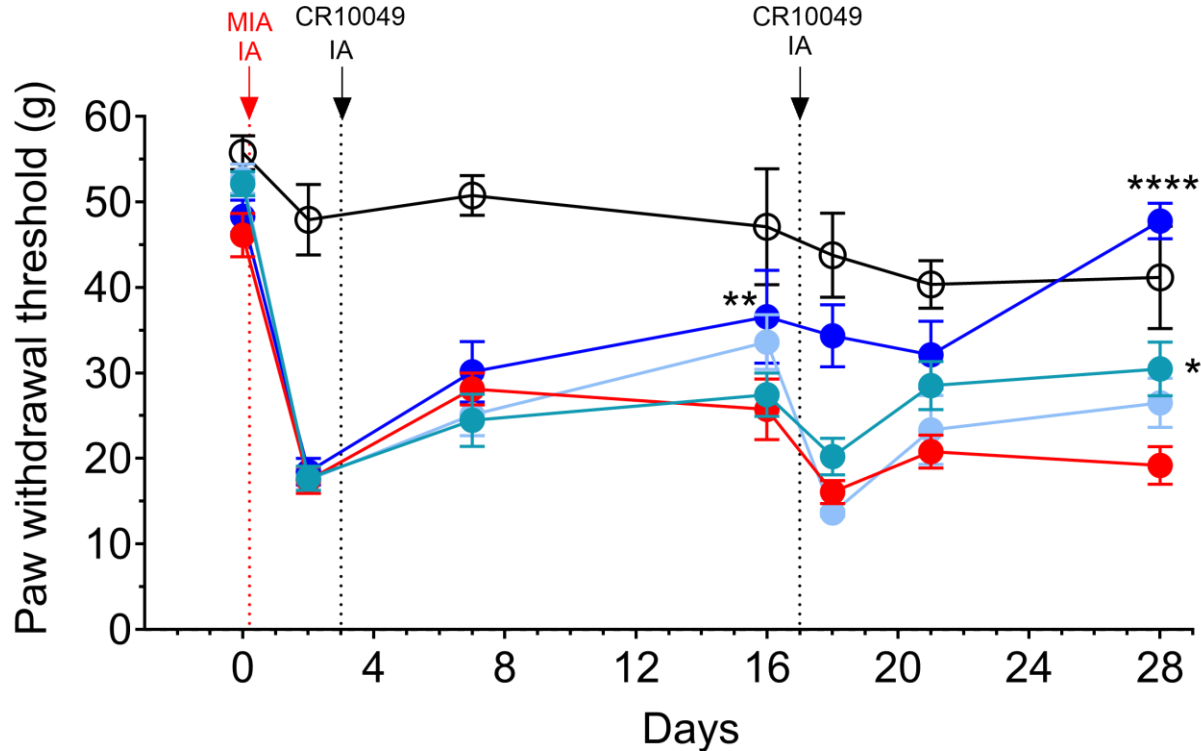
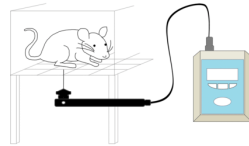


Mean ± SEM. One way ANOVA with Tukey's multiple comparisons test.
 *** p < 0.001, **** p < 0.0001

CR10049 completely abolishes inflammatory OA pain in MIA rats



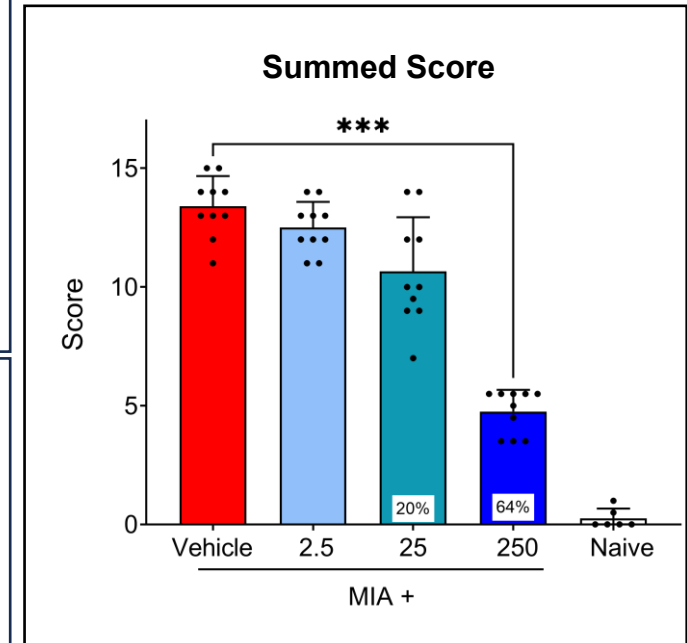
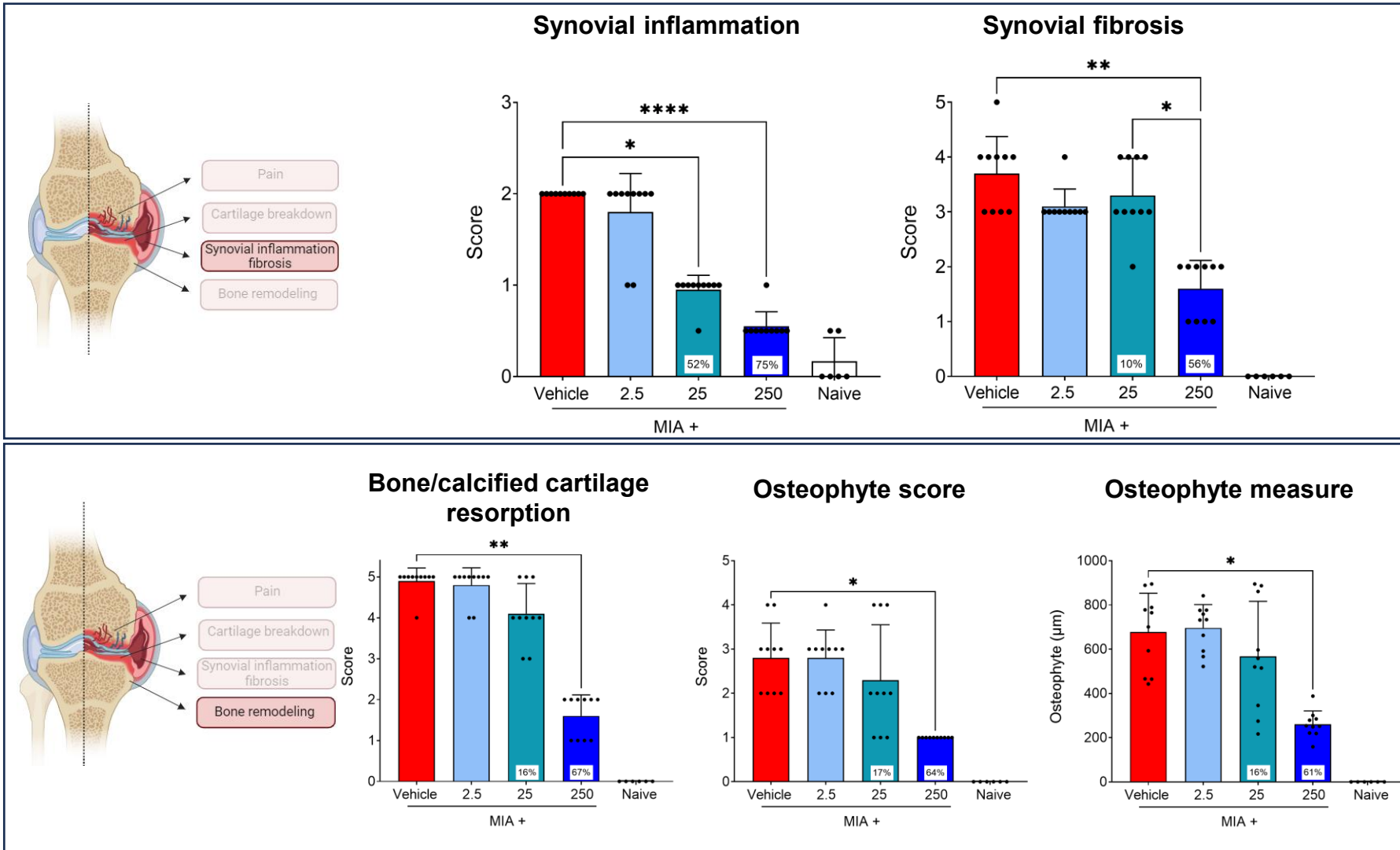
Evoked pain - eVon Frey



- At D28 CR10049 250 µg = 98% pain reduction
- Evidence of dose-response

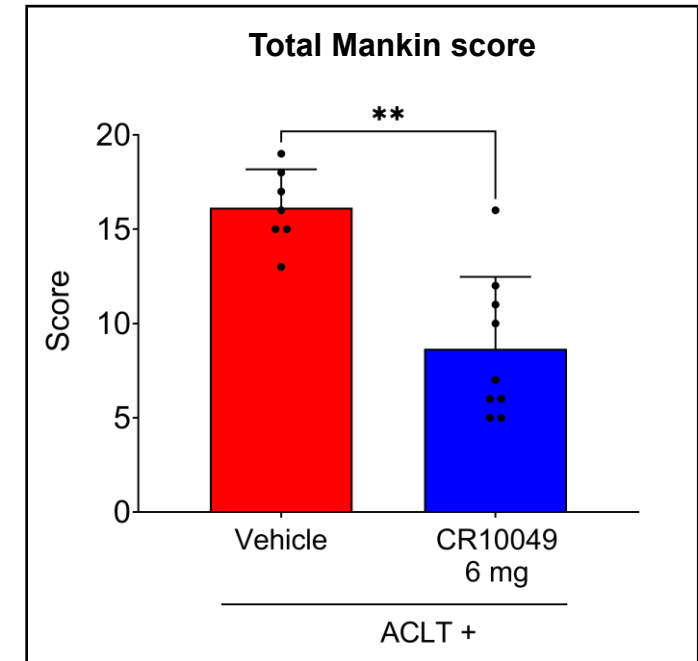
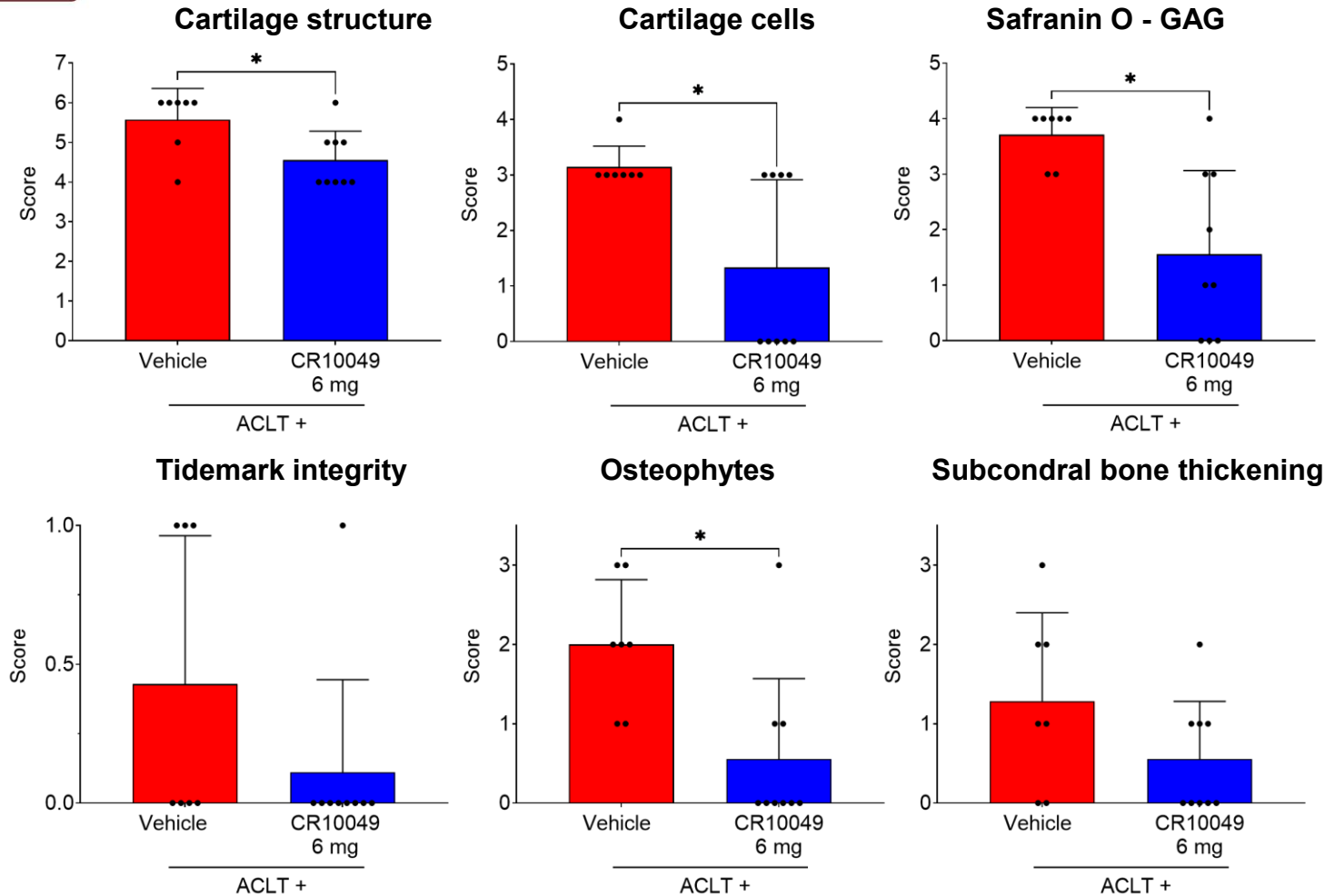
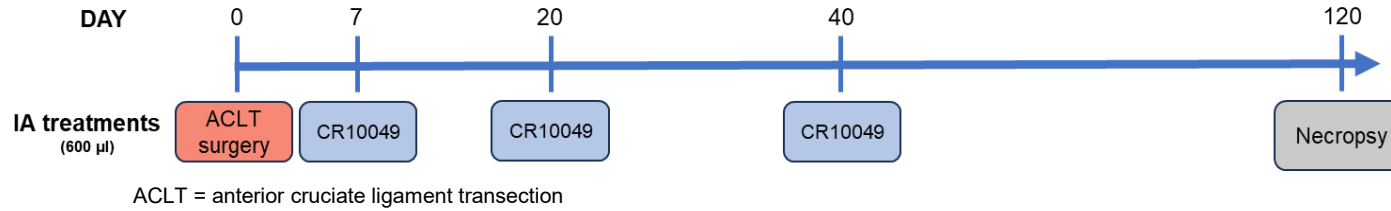
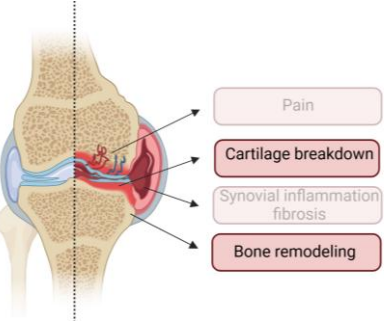
MIA: Monoiodoacetate (2 mg)
 n=10/group, naïve n=6. Mean ± SEM. Two way ANOVA with Dunnett multiple comparisons test
 CR10049 vs Veh: * p<0.05, ** p<0.01, **** p<0.0001

CR10049 improves joint structure in a rat OA inflammatory model (MIA)



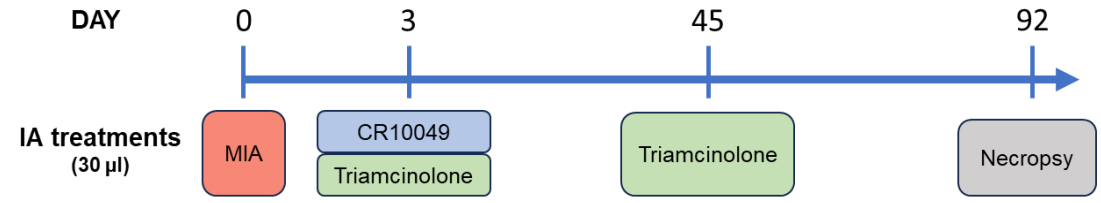
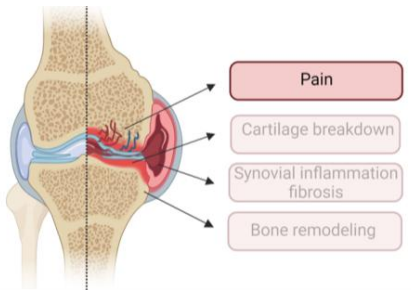
Mean ± SD. One way ANOVA Kruskal–Wallis with Dunn's multiple comparisons test; *, p<0.05, ** p<0.01. % of decrease compared to vehicle within the bar graph

CR10049 improves joint structure in a rabbit surgical OA model (ACLT)

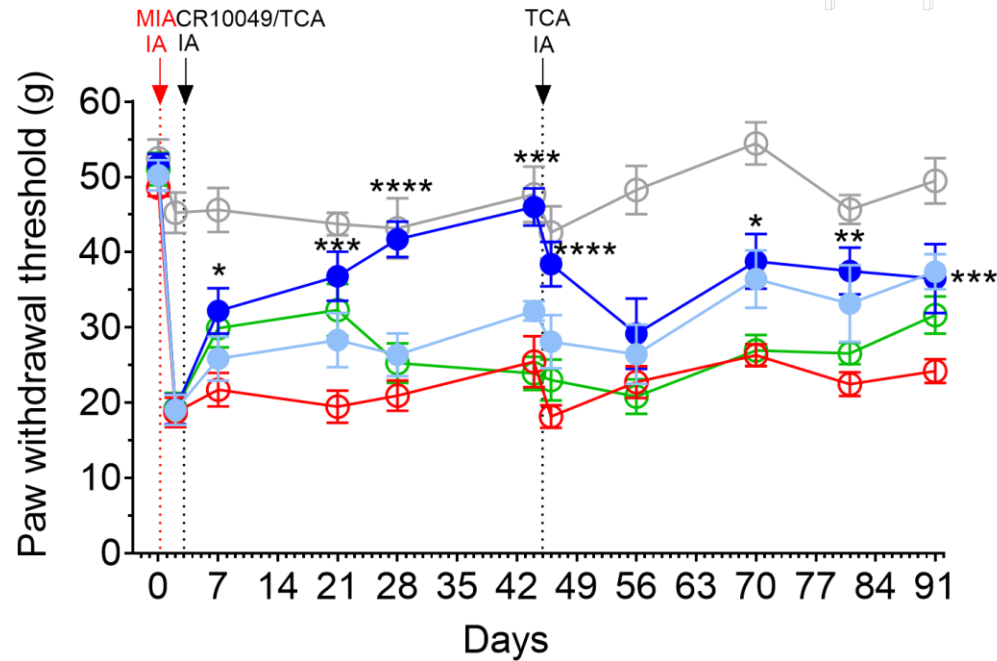
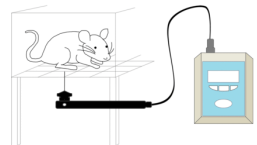


Vehicle n=7, CR10049 n=9. Mean ± SD. Mann-Whitney test; ** p<0.01.

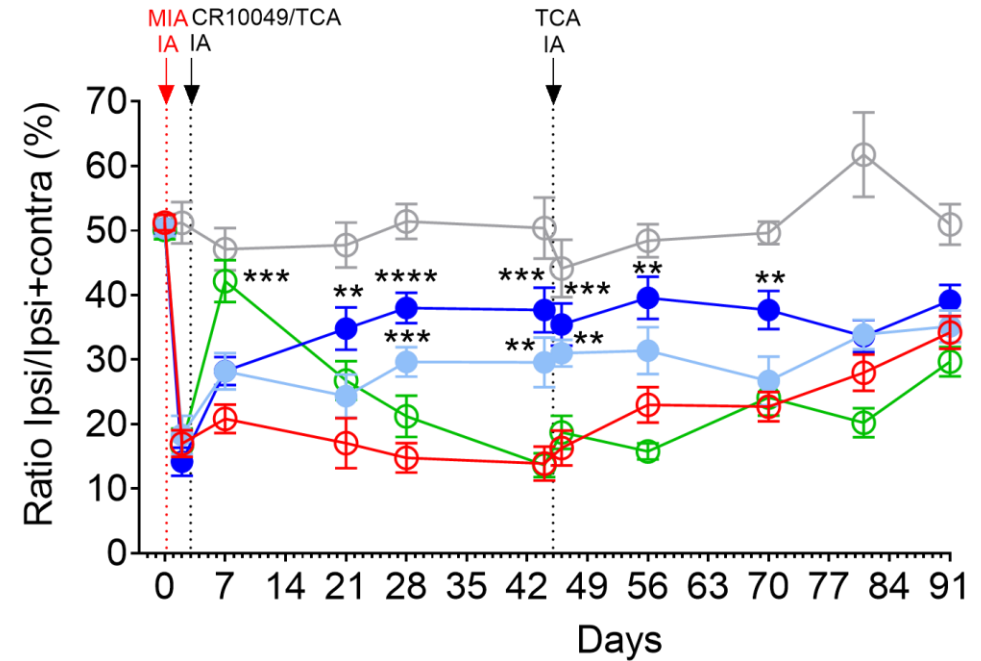
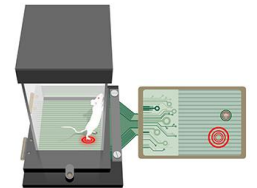
Remarkably, CR10049 has a long-acting effect in reducing MIA-induced OA pain



Evoked pain – Electronic Von Frey



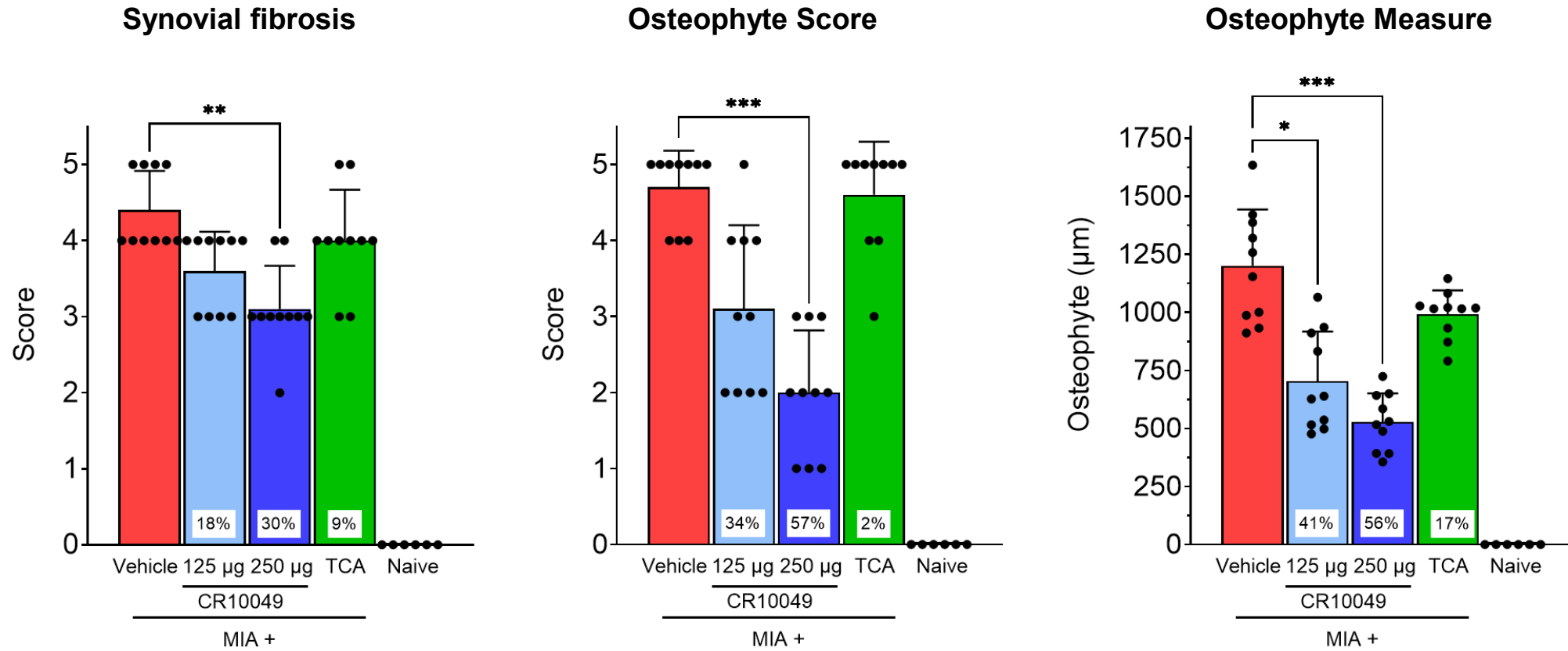
Non-evoked pain – Dynamic Weight Bearing



Naive
 MIA+Vehicle
 MIA+CR10049 125 µg
 MIA+CR10049 250 µg
 MIA+TCA

TCA: triamcinolone acetonide
 MIA: Monoiodoacetate (2 mg)
 n=11/group, naïve n=6. Mean ± SEM. Two way ANOVA with Tukey's multiple comparisons test
 CR10049 vs Veh: * p<0.05, ** p<0.01, *** p<0.001

CR10049 improves the joint structure in the 3-months rat MIA model



n=11/group; n=6/naive. Mean ± SD. One way ANOVA Kruskal–Wallis with Dunn’s multiple comparisons test; *p<0.05, ** p<0.005, *** p<0.001. % of decrease compared to vehicle within the bar graph.

Conclusions

- ▶ CR10049 is a small molecule multi-kinase inhibitor, preferentially targeting **SRC family members**
- ▶ CR10049 inhibits inflammation as well as degradation in *in vitro* OA models
- ▶ In a **small animal inflammatory OA model** (rat MIA) :
 - ▶ CR10049 significantly reduces **OA pain** and improves the **joint structure**: the effect is long-lasting (3 months) after a single IA injection
- ▶ In a **large animal surgical model** (rabbit ACLT):
 - ▶ CR10049 shows a significant effect on **joint structure**, reducing cartilage degradation and osteophytes formation
- ▶ No toxic effects were observed when injected systemically (IV) up to 60 mg/kg and locally (IA) up to 5 mg (i.e. a 20x higher dose than the maximum effective dose) in rats

CR10049

- the first intra-articular compound with a beneficial long-acting effect on inflammatory OA pain and joint structure
- a good candidate for the treatment of the OA inflammatory phenotype

Acknowledgements

ROTTAPHARM BIOTECH

Monza, Italy

Lucio Rovati

Roberto Artusi

Gianfranco Caselli

Matteo Ghirri

Tiziana Piepoli

Michela Visintin

INOTIV

Boulder, CO - USA

Alison Bendele

AGINKO

Marly, Switzerland

Pierre Mainil-Varlet

Thank you for your attention